Genetic Aspects of Epilepsy

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List of Abbreviations

3D	Three dimensional
3DSSP	3D stereotactic surface projection
Ach	Acetyl Choline
AchR	Acetylcholine receptor
AD	Autosomal dominant
ADNFLE	Autosomal Dominant Nocturnal Frontal Lobe Epilepsy
ADPEAF	Autosomal dominant partial epilepsy with auditory features
AEDs	Antiepileptic drugs
AES	American Epilepsy Society
AMT	a-11Cmethyl-Ltryptophan
AMTR	Antero-medial-temporal resection
AR	Autosomal recessive
ARX	Aristaless related homeobox gene
AS	AngelmanSyndrome
BECTS	Benign epilepsy with centrotemporal spikes
BFNC	Benign Familial Neonatal Convulsions
BFNIS	Benign familial neonatal-infantile seizures
CAE	childhood absence epilepsy
CDG	Congenital disorder of glycosylation
CMA	Chromosomal microarray analysis
CNS	Central nervous system
CNVs	Copy number variations
CPR	Crude lifetime prevalence rate
CRS	Cortical responsive stimulation
CT	Computed tomography
DBS	Deep brain stimulation
DEPDC5	DEP domain containing protein 5
DTI	Diffusion tensor imaging
EEG	Electroencephalography
EIEE	Early infantile epileptic encephalopathy
EIME	Early infantile myoclonic epilepsy

List of Abbreviations(Cont.)

ETNS	External trigeminal nerve stimulation
FCD	Focal cortical dysplasia
FDG-PET	Fluorodeoxyglucose PET scanning
FFEVF	Familial focal epilepsy with variable foci
FISH	Fluorescent in situ hybridization
FLTLE	Familial lateral temporal lobe epilepsy
FMRI	Functional magnetic resonance imaging
FMZ	Flumazenil
GABA	Gama amino butyric acid
GEFS+	Genetic epilepsy with febrile seizures plus
GTC	Generalized tonic clonic
ILAE	International League Against Epilepsy
IPSCs	Induced pluripotent cells
JAE	Juvenile absence epilepsy
JME	Juvenile myoclonic epilepsy
LCM	Lacosamide
LGI1	Leucine rich glioma inactivated 1 protein
LKS	Landau Kleffner syndrome
LOCOE	Late onset childhood occipital epilepsy
Mb	Megabases
MELAS	Myopathy, encephalopathy, lactic acidosis, and stroke like episodes
MRS	Magnetic resonance spectroscopy
MSI	Magnetic source imaging
MST	Multiple subpial transection
MTLE HS	Mesial temporal lobe epilepsy with hippocampal sclerosis
mTOR	Mammalian target of rapamycin
NAA	N-acetyl-aspartate
Nach	Nicotinic acetylcholine
NCLS	Neuronal ceroid lipofusinosis
NGS	Next generation sequencing

List of Abbreviations(Cont.)

NINDS	National Institute of Neurological Disorders and Stroke
NK1	Neurokinin-1 receptor
NMDA	N-methyl-D-aspartate
P5P	Pyridoxal-5-phosphate
PCDH19	*Protocadherin-19*
PDS	Paroxysmal depolarization shift
PET	Positron emission tomography
PHT	Phenytoin
PLCB1	Phospholipase C beta-1
PME	Progressive myoclonic epilepsies
PNPO	Pyridoxine 5′-phosphate oxidase
PWS	Prader WilliSyndrome
RNS	Responsive neurostimulation
SMEI	Severe myoclonic epilepsy of infancy
SNP	Single nucleotide polymorphism
SPECT	Single photon emission computerized tomography
SPM	Statistical parametric mapping
STXBP1	The syntaxin binding protein 1 gene
TLE	Temporal lobe epilepsy
TS	Tuberous sclerosis
TSC	Tuberous sclerosis complex
UDP	Uridine-5-prime-diphosphat
VNS	Vagal nerve stimulation
VUS	Variant of unknown significance
WES	Whole exome sequencing
WGS	Whole genome sequencing

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Introduction

Epilepsyis a group of neurological disorders characterized by epileptic seizures(**Chang and Lowenstein, 2003; Fisher, et al., 2014)**.

Epileptic seizures are episodes that can vary from brief and nearly undetectable to long periods of vigorous shaking **(Fisher, et al., 2014)**.

In epilepsy, seizures tend to recur, and have no underlying known cause.While seizures that occur due to a specific cause are not deemed to represent epilepsy **(Eadie, 2012).**

Epilepsy is one of the most common serious neurological disordersaffecting about 65 million people globally **(Thurman, et al., 2011).**

It is more common in males than females with the overall difference being small. Most of those with the disease (80%) are in the developing countries **(Newton, 2012).**

In the developed countries, epilepsy most commonly starts either in the young or in the old age groups. In the developing countries, its onset is more common in older children and young adults due to the higher rates of trauma and infectious diseases **(Newton, 2012).**

Central nervous system (CNS) infections are the main cause of seizures and acquired epilepsy in the developing world. Acute seizures are common in severe

meningitis, viral encephalitis, malaria, and neuro-cysticercosis, and in most cases are associated with increased mortality and morbidity including subsequent epilepsy. Neuronal excitability secondary to pro-inflammatory signals induced by CNS infections are an important common mechanism for the generation of seizures **(Developmental Medicine and Childhood Neurology, 2011).**

Epilepsy can have both genetic and acquired causes, with interaction of these factors in many cases. Established acquired causes include serious brain trauma, stroke, tumors and problems in the brain as a result of a previous infection **(Newton, et al., 2012).**

Genetics is believed to be involved in the majority of most epileptic cases either directly or indirectly. Some epilepsies are due to a single gene defect (1-2%); most are associated with the interaction of multiple genes and environmental factors **(Pandolfo, 2011).**

Most involved genes affect ion channels, either directly or indirectly. These include genes for ion channels themselves, enzymes, GABA, and G protein-coupled receptors **(Simon, et al., 2012).**

In identical twins, if a co-twin is affected there is a 50-60% chance that the other will also be affected. In non-identical twins the risk is 15%.These risks are greater in those with generalized rather than with partial seizures. If both co-twins are affected, most of the time they have the same epileptic type (70-90%)**(Pandolfo, 2011).**

Between 1 and 10% of those with Down syndrome and 90% of those with Angelman syndrome have epilepsy **(Bhalla, et al., 2011).**

Epilepsy cannot usually be cured, but medications can control seizures effectively in about 70% of cases. (**Bergey, 2013).**

A poor outcome is related to some factores which include little response to the initial treatment, generalized seizures, a family history of epilepsy, psychiatric problems, and waves on the EEG representing generalized epileptiform activity (**Kwan, and Patrick, 2012).**

People with epilepsy in general are at an increased risk of death. This increase is between 1.6 and 4.1 fold greater than that of the general population and is often related to: the underlying cause of the seizures, status epileptics, suicide, trauma, and sudden unexpected death in epilepsy (SUDEP) **(Hitiris, et al., 2007).**

Aim of the Work

The aim of the work is to review the causes, diagnosis and management of epilepsy from the genetic aspect of view.

Definitions

Seizures and epilepsy are not the same. Epilepsy is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. A seizure is an event of a sudden surge of electrical activity in the brain and epilepsy is the disease involving recurrent unprovoked seizures**(Robert, and Fisher, 2014).**

Epilepsy:

According to International League Against Epilepsy (ILAE), the new definition of epilepsy should fulfill the following:

A person is considered to have epilepsy if expresses any of the following conditions:

1- At least two un provoked (or reflex) seizures occurring more than 24 hours apart.
2- One un provoked (or reflex) seizures and there is high risk of having further seizure in the future.
3- Diagnosis of an epilepsy syndrome such as benign epilepsy with central temporal spikes" previously known as benign rolandic epilepsy".

Item 2 allows a condition to be considered epilepsy after one seizure if there is a high risk of having another seizure. Often, the risk will not precisely be known and so the old definition will be employed, i.e., waiting for a second seizure before diagnosing epilepsy.

Epilepsy is considered to be resolved for individuals who had an age dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure free for the last 10 years, with no seizure medications for the last 5 years**(Robert, and Fisher, 2014).**

An epileptic seizure:

An epileptic seizure: is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain **(Robert, and Fisher, 2014).**

Seizures can result in convulsions (An abnormal, involuntary contraction of the muscles) and loss of consciousness. Examples of possible manifestations of seizures are affection of personality, mood, memory, sensation, and/or movement. Other possible manifestations are Blank stares, lip smacking, intermittent eye movements, and jerking movements of the extremities **(Cowan, 2002).**

Convulsion:

The term "convulsion" is a popular unofficial term used to mean substantial motor activity during a seizure. Such activity might be tonic, clonic or tonic-clonic. In some languages convulsions and seizure may be considered synonyms **(Fisher, et al., 2014).**

Provoked seizure:

Provoked seizure: is a seizure that occurs in reaction to an acute, transient condition affecting the brain. Provoking factors include, but are not limited to, head

traumas, stroke, intracranial infections, acute metabolic disturbances (e.g., hypoglycemia, anoxia) and acute toxin or drug poisoning **(Tamber and Mountz, 2012).**

Epileptic syndrome:

An epileptic syndrome is a disorder that manifests one or more specific seizure types and has a specific age of onset and a specific prognosis. Several types of epileptic syndromes can be distinguished. In general, seizure type is the primary determinant of the type of medications the patient is likely to respond to, and the epilepsy syndrome determines the type of prognosis which could be expected **(Tamber and Mountz, 2012).**